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Update on Glucose Management Among Noncritically Ill Patients Hospitalized on Medical and Surgical Wards

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Hyperglycemia is a common issue affecting inpatient care. Although this is in part because of the higher rate of hospitalization among patients with preexisting diabetes, multiple factors complicate inpatient glucose management, including acute stress from illness or surgery, erratic dietary intake, and contribution of medications. It has been repeatedly demonstrated that poorly controlled blood glucose levels are associated with negative clinical outcomes, such as increased mortality, higher rate of surgical complications, and longer length of hospital stay. Given these concerns, there has been extensive study of the optimal strategy for management of glucose levels, with the bulk of existing literature focusing on insulin therapy in the intensive care unit setting. This review shifts the focus to the general adult medical and surgical wards, using clinical guidelines and sentinel studies to describe the scientific basis behind the current basal-bolus insulin-based approach to blood sugar management among noncritically ill inpatients. Patient-centered clinical trials looking at alternative dosing regimens and insulin analog and noninsulin agents, such as glucagon-like peptide-1 agonist therapies, introduce safe and effective options in the management of inpatient hyperglycemia. Data from these studies reveal that these approaches are of comparable safety and efficacy to the traditional basal-bolus insulin regimen, and may offer additional benefit in terms of less monitoring requirements and lower rates of hypoglycemia. Although existing data are encouraging, outcome studies will be needed to better establish the clinical impact of these more recently proposed approaches in an effort to broaden and improve current clinical practices in inpatient diabetes care.

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Hyperglycemia is very common in the inpatient setting and may be caused by a combination of preexisting diabetes, acute physiologic stress, and medications [1, 2]. Furthermore, hyperglycemia is associated with worse outcomes in the inpatient setting, such as increased mortality, increase in surgical complications, and longer length of stay, especially in patients not known to have diabetes [3–5]. Inpatient management of diabetes is challenging, in part because of multiple comorbidities [3]. Patients with diabetes have increased risk of cardiovascular disease, renal disease, and infection, among other disorders, and this translates to a greater incidence of hospitalization and longer length of stay compared with patients without diabetes [3, 6, 7]. Recognizing the broad and substantial impact that diabetes and hyperglycemia have on today's health care has therefore prompted many studies of the management of glucose in the inpatient setting.

Management of hyperglycemia in the intensive care unit (ICU) has been extensively studied and reviewed [8–10]. However, less information is available on the best approach to patients outside the ICU. As demonstrated in the 2009 Normoglycaemia in Intensive Care

Abbreviations: CI, confidence interval; GLP-1, glucagon-like peptide-1; GV, glycemic variability; ICU, intensive care unit; NPH, neutral protamine Hagedorn; POC, point-of-care; RABBIT 2 Trial, Randomized Study of Basal-Bolus Insulin Therapy in the Inpatient Management of Patients With Type 2 Diabetes; SSI, sliding scale insulin; TPN, total parenteral nutrition.

Evaluation and Survival Using Glucose Algorithm Regulation study, an intravenous insulin infusion is successful at maintaining glucose in a predetermined range in the ICU; however, it is not practical outside of a critical care setting because of the intensity of nursing support required [11]. In this review, we will focus on use of insulin and noninsulin agents for glucose control in the general adult medical and surgical wards, highlighting outcome studies, treatment trials, and remaining controversies in management. Specific issues addressed here will include the relationship of glucose levels to outcomes, ideal targets for glucose, and optimal medical management of blood glucose levels.

1. Historical Perspective

In a 2004 seminal review by Clement *et al.* [6], the question of what constitutes optimal glucose control was investigated. The concept of blood glucose threshold levels was addressed in terms of mortality outcomes across different medical and surgical fields. Data collected by Umpierrez *et al.* [12] from 1886 admissions found that 12% of these patients demonstrated new hyperglycemia (defined by fasting blood glucose ≥ 126 mg/dL or random blood glucose ≥ 200 mg/dL on two or more occasions and no history of diabetes), a finding that was associated with an 18-fold increase in inpatient mortality compared with normoglycemic patients. These patients were also found to have longer hospital stays, greater likelihood of need for a critical care setting, and higher rate of transitional care. A meta-analysis by Capes *et al.* [13] compared the relative risk of inpatient mortality after myocardial infarction in patients with and without diabetes in relation to admission blood glucose levels. Patients with diabetes with admission glucose ≥ 180 mg/dL were found to have a moderately increased relative risk at 1.7 [95% confidence interval (CI), 1.2 to 2.4] for inpatient mortality compared with those patients with diabetes and glucose values below this threshold. Among patients without diabetes, admission glucose values of 110 to ≥ 144 mg/dL were associated with a substantial increase in relative risk of inpatient mortality (3.9; 95% CI, 2.9 to 5.4). Of note, the ranges of blood glucose used in these results were based on varying cutoffs among studies included in the meta-analysis.

Hyperglycemia has also been found to correlate with postoperative complications, and studies have shown that controlling glucose levels improves morbidity and mortality among surgical patients [14–20]. Based on this known association, Wang *et al.* [21] conducted a cohort study with >6600 patients undergoing general and vascular surgery to investigate a correlation between preoperative glucose and postoperative infection. The sample excluded known patients with diabetes and those with preoperative sepsis. The study authors found that rates of infection after surgery were significantly lower in those patients with preoperative glucose levels within a lower range (5.62%, $P < 0.001$ for glucose of 70 to 99 mg/dL) than in those with levels of 100 to 139 mg/dL (9.33%) and 140 to 179 mg/dL (10.16%). Although these data, and those from the Capes *et al.* review [13], are observational, and thus subject to the usual limitations, they do offer a solid physiologic rationale for the strong association between hyperglycemia and poor outcomes. In addition, this association is consistent across patient populations and disease states and includes endothelial dysfunction, impaired tissue perfusion, prothrombotic state, increased platelet aggregation, and left ventricular dysfunction [22–26].

2. Why Insulin?

When considering how to manage hyperglycemia, insulin is generally accepted as the primary therapy for achieving glucose control [6] based on several studies showing an association between insulin treatment and improved patient outcomes [18, 27]. The traditional thought has been that this was related to the effect on blood glucose levels; however, small supporting studies have since shown pleiotropic effects independent of glucose lowering results, including improved myocardial perfusion [28], decreased blood pressure [29, 30], and decreased heart failure [31]. With knowledgeable prescribing providers, insulin can be matched to

rapidly changing patient needs because of dose flexibility and multiple types with different durations of action—especially in the setting of variable and unpredictable nutrition. Because insulin does not have drug interactions, it is particularly desirable in the hospital where other medications are being added or discontinued rapidly.

3. Improving on Tradition

Insulin is often described in terms of its pharmacokinetic and pharmacodynamic properties and typically categorized as basal, prandial, or correctional. Although basal insulin, meant to match endogenous insulin production in a fasting state, describes long-acting formulations with minimal daily variation, prandial and correctional insulins are short-acting and are used to address glucose peaks that occur after food ingestion or to correct hyperglycemia to an ideal range, respectively [32, 33].

Outside of the ICU, glucose has frequently been managed with correctional insulin only (the traditional sliding scale), rather than in combination with basal insulin and prandial insulin [34]. However, this may not be the most appropriate approach for inpatient hyperglycemia management, a claim supported by findings from a prospective cohort study by Queale *et al.* [35]. Using data from 171 medical inpatients with diabetes, study investigators discovered that individuals receiving monotherapy with correctional insulin had a threefold higher risk of hyperglycemia than those not on any pharmacologic diabetes treatment ($P < 0.05$). Although conclusions are limited from this observational study, the data did demonstrate a lack of benefit from regimens using only sliding-scale insulin, and subsequent studies have since provided additional evidence supporting newer, alternative regimens.

One such study is the 2007 Randomized Study of Basal-Bolus Insulin Therapy in the Inpatient Management of Patients With Type 2 Diabetes (RABBIT 2 Trial), a prospective controlled investigation by Umpierrez *et al.* [36] comparing the efficacy and safety of a basal-bolus regimen with the traditional sliding-scale regimen using correctional doses of insulin in 130 insulin-naïve patients with known type 2 diabetes admitted to general medicine services (ICU patients were excluded). Patients were randomized to a regimen consisting of daily glargine and mealtime glulisine with correctional glulisine (basal bolus) using weight-based initial dosing and a titration algorithm or glulisine only for correction of blood sugars according to a sliding scale insulin (SSI). The study authors found that those patients in the basal-bolus group had lower fasting blood sugars (147 ± 36 mg/dL vs SSI 165 ± 41 mg/dL, $P < 0.01$), lower lengths of stay, and greater prevalence of achieving goal glucose levels (blood sugar 70 to 140 mg/dL) with 66% at goal within the basal-bolus regimen as compared with 38% in the SSI group. Incidence of hypoglycemia, defined as blood sugar <60 mg/dL, was equal between the two groups and acceptably low at two patients each. Although admittedly underpowered to determine change in other outcomes, such as mortality, this study did demonstrate greater glycemic control without increased hypoglycemia in the basal-bolus group.

A follow-up study in 2011 by Umpierrez *et al.* [7] again compared the efficacy of a basal-bolus regimen to a sliding-scale protocol, this time among surgical patients, with end points including postoperative complications (wound infection, pneumonia, bacteremia, and respiratory or acute renal failure) in addition to daily blood glucose levels. Unlike those patients in the original RABBIT 2 trial, participants in RABBIT 2 surgery were not necessarily insulin-naïve. Target glucose range was 100 to 140 mg/dL in this study. In addition to finding lower blood glucose levels in the basal-bolus group (145 ± 32 mg/dL compared with 172 ± 47 mg/dL in the sliding-scale group), study authors found a substantial reduction in composite outcomes, which included pneumonia, bacteremia, wound infection, and respiratory and renal failure, from those on the sliding-scale regimen (24.3%) compared with those on the basal-bolus regimen (8.6%) ($P = 0.003$). This is the only randomized trial looking at hard outcomes beyond glucose control outside of the ICU setting. There was a higher incidence of mild hypoglycemic events in this study compared with the RABBIT 2 medicine trial, with 23.1% of patients in the basal-bolus group and 4.7% of patients in the sliding-scale group having a recorded glucose level <70 mg/dL ($P < 0.001$). Severe hypoglycemia

(glucose <40 mg/dL) occurred in 3.8% of the basal-bolus group and in none of the SSI group. Possible explanations for this higher rate compared with the medicine trial include reduced nutritional intake among surgical patients, and most patients in the surgical trial were on a higher total daily dose of insulin (0.5 U/kg/d compared with 0.4 U/kg/d, respectively) than most of the patients in the medicine trial.

In the Basal Plus trial, Umpierrez *et al.* [37] investigated the necessity of scheduled prandial insulin for inpatient glycemic control. The study looked at 375 patients admitted to medical or surgical services with a known history of type 2 diabetes who were randomly assigned to three treatment arms: a basal-bolus regimen with scheduled premeal and corrective short-acting glulisine in addition to long-acting glargine, a basal plus regimen consisting of glargine along with corrective glulisine, and a third arm using a corrective scale for blood glucose levels >140 mg/dL without basal insulin. Patients were targeted to blood glucose goal range of 100 to 140 mg/dL, and if treatment failure was encountered in the basal plus or corrective scale group (defined as a mean daily blood glucose >240 mg/dL or consecutive blood glucose levels >240 mg/dL), patients were advanced to the basal-bolus regimen. The study found that both the basal-bolus and basal plus regimens had lower mean daily blood glucose levels than the corrective-only regimen ($P = 0.04$) and that the improvement in mean daily blood glucose after the first day of treatment was similar between the two basal-containing regimens. These two regimens also were found to have less treatment failure than the corrective regimen. There was no difference among the three groups regarding incidence of severe hypoglycemia (defined as blood glucose <40 mg/dL); however, mild hypoglycemia (blood glucose <70 mg/dL) was higher in the basal-bolus regimen (16%) than the basal plus (13%) and corrective-only regimens (3%, $P = 0.02$). Given the similar efficacy between the two basal-containing regimens, and overall improvement in glycemic control relative to the corrective insulin regimen, the study concluded that basal insulin should be included in glucose treatment plans and that a modified regimen such as basal plus offers similar control compared with the traditional basal-bolus regimen.

Haw *et al.* went on to investigate the effect of these two regimens on glycemic variability (GV), calculated using the mean daily standard deviation of blood glucose values, the mean daily range of blood glucose (average daily GV), and the mean amplitude of glycemic excursions [38–41] in a *post hoc* analysis of the Basal Plus trial [42]. Looking at data from 279 general medicine and surgery patients, the analysis revealed no substantial difference in GV between the basal plus and basal-bolus groups. Interestingly, surgical patients in the basal-bolus group compared with their surgical cohort in the basal plus group were found to have a statistically significant higher GV. Of note, the degree of GV did not seem to correlate with the rate of hospital complications; therefore, its clinical significance is not established.

4. Human or Analog

Recombinant human insulins are available in short-acting and intermediate-acting formulations. However, they are not as well matched to basal and prandial needs as the newer analog insulins, which are available in more rapid-acting and longer-acting formulations, the latter of which avoids the insulin peak that often complicates glucose management. Analog insulins are, however, more expensive than their human insulin counterparts, thus creating a dilemma for hospitals. These different factors must all be considered to determine the best types of insulin for inpatient use. In a multicenter trial of 130 patients admitted to a general medicine service, the safety and efficacy of a regimen using insulin analogs was compared with one using human insulins [43]. For this study, patients with type 2 diabetes and blood glucose levels between 140 and 400 mg/dL were randomized to either a basal-bolus (analog insulins) regimen with daily detemir and premeal aspart or a split-mixed protocol using twice-daily injections of neutral protamine Hagedorn (NPH) and regular insulin (human insulins). Initial dosing was based on a weight-based regimen for both groups. Patients were restricted to those with blood glucose levels between 140 and 400 mg/dL, at least a 3-month known history of type 2 diabetes, and absence of diabetic ketoacidosis. By treating to goal blood

glucose levels between 60 (threshold for hypoglycemia) and 140 mg/dL, study authors discovered similar glycemic improvement between the detemir and NPH groups, with pre-treatment blood glucose levels of 228 ± 54 mg/dL and 223 ± 58 mg/dL ($P = 0.61$) improving to 160 ± 38 mg/dL and 158 ± 51 mg/dL ($P = 0.8$), respectively, after the first day of therapy. In addition, no significant difference was found between the two groups in terms of number of patients experiencing an episode of hypoglycemia ($P = 0.20$) and frequency of hypoglycemic blood glucose readings ($P = 0.86$). Based on these findings, the study authors concluded there were no statistical differences in efficacy, as measured by improvement in mean daily blood glucose levels, or safety, as determined by hypoglycemia incidence, between the analog regimen of detemir/aspart and a human insulin regimen of NPH/regular. This study had important implications for hospitals concerned with higher cost of analog insulins.

5. Hypoglycemia

Turchin *et al.* [44] looked at the effect inpatient hypoglycemic events had on patients in a 2009 retrospective, cohort study of 4368 admissions in 2500 patients with diabetes. Both the number and severity of hypoglycemic events, defined as a glucose level <50 mg/dL, were evaluated, as were length of stay and mortality (inpatient and 1-year after discharge). The study found a 7.7% incidence of hypoglycemia among the admissions and, through a multivariable analysis, discovered that each additional day with hypoglycemia was associated with an 85.3% increase in odds of an inpatient death ($P = 0.009$); this risk rose three times for every 10 mg/dL decrease in the lowest blood glucose during hospitalization ($P = 0.0058$). There was also a 65.8% increase in odds of death within 1 year after discharge ($P = 0.0003$) with each additional day of hypoglycemia. As for length of stay, this was increased by 2.5 days for each day with hypoglycemia ($P < 0.0001$). Further, multiple studies have also demonstrated a positive association between mortality and hypoglycemia [45–47].

Although the mechanism behind the relationship between hypoglycemia and mortality remains unclear, possible explanations include the proinflammatory state of hypoglycemia and sympathetic nervous stimulation, subsequently leading to arrhythmias and ischemia [46, 48, 49]. Furthermore, the context of hypoglycemia may be important, with several studies finding higher mortality rates associated with spontaneous hypoglycemia compared with that induced with insulin therapy [50–52]. This suggests underlying severe illness, such as multiorgan failure, is contributing to these higher rates. Finally, in severe hypoglycemia, neurologic complications such as seizure with aspiration may cause additional damage [53].

A retrospective cohort study by Garg *et al.* [54] went on to investigate whether the relationship between hypoglycemia and mortality was associated with insulin use. Using inpatient data from 2008 to 2010, the study authors examined the prevalence of mortality across four separate groups, according to presence of hypoglycemia (defined as blood sugar ≤ 50 mg/dL) and treatment with insulin. Study findings were notable for a significantly higher mortality among those patients with insulin-treated hypoglycemia compared with the insulin-treated controls (20.3 vs 4.5%, $P < 0.0001$). Noninsulin-treated hypoglycemia was similarly associated with greater mortality than seen among noninsulin-treated controls (34.5 vs 1.1%, $P < 0.0001$). Interestingly, those in the noninsulin-treated hypoglycemia group experienced higher mortality rates than those in the insulin-treated hypoglycemia group ($P < 0.0001$); however, the opposite was found among the controls, with significantly lower mortality in the noninsulin-treated control group compared with the insulin-treated control group ($P < 0.0001$). These findings demonstrate an association between hypoglycemia and mortality and go on to illustrate a stronger effect of spontaneous (noninsulin treated) hypoglycemia on mortality compared with insulin-associated hypoglycemia. This latter finding, which has been described previously, may be the result of other contributing factors, such as malnutrition or malignancy, in cases of spontaneous hypoglycemia that could account for a worse prognosis.

The risk of hypoglycemia in relation to the particular regimen insulin dosing was then assessed in a retrospective, case-control study by Rubin *et al.* [55] in 2011. Of 1990

hospitalized patients with a diagnosis of diabetes selected for the study, half were defined as cases, as determined by a point-of-care (POC) glucose <70 mg/dL after the first 24 hours of admission. Controls were defined by a POC glucose ≥ 70 mg/dL and matched to each case on the basis of hospital day of hypoglycemia, age, sex, and body mass index. The insulin doses administered during the 24-hour period prior to hypoglycemia in the cases, and matched POC in the controls, were then evaluated in terms of dose per body weight and type of insulin exposure. The latter was categorized among four different regimens: glargine plus any other insulin, NPH plus any other insulin, lispro and/or regular insulin only, and no insulin. The authors found that the odds of hypoglycemia (adjusted for insulin regimen, SSI use, and albumin, creatinine, and hematocrit) were not increased by increasing insulin dosing within a range of 0.2 to 0.6 U/kg/d. However, odds of hypoglycemia were higher among patients receiving insulin doses >0.6 U/kg/d.

6. Noninsulin Agents: Why Not?

In addition to these observed benefits, insulin has also been the longstanding preferred agent to treat inpatient hyperglycemia because of limitations of other therapies. Metformin, although a recommended first-line medication for treatment of type 2 diabetes [56], is discouraged in patients with conditions that predispose toward central hypoxia, such as pulmonary, cardiac, or renal impairment, because of the concern for increased risk of lactic acidosis, a rare but serious complication of metformin therapy [57]. Other contraindications to metformin use include severe liver disease, alcohol abuse, and concurrent use of potentially renal toxic intravenous radiographic contrast agents, all of which limit its applicability in the hospital setting [58, 59].

Sulfonylureas are another commonly used oral agent for type 2 diabetes; however, because insulin secretagogues, these medications can cause hypoglycemia, and unlike insulin, their dosing is less flexible, and onset and duration of action can be less predictable. Considering the risk of hypoglycemia is increased in those with erratic or poor oral intake, or those with hepatic or renal impairment, all of which may be encountered more frequently in hospitalized patients, sulfonylureas are not considered preferred agents for inpatient glycemic control [2, 56, 57]. Thiazolidinediones, which act as insulin sensitizers, have a substantial delay in onset of action [56]. These drugs are associated with peripheral edema and precipitation or exacerbation of heart failure [57]. Considering these described limitations for treatment alternatives, insulin established itself as the recommended and most widely used agent for glucose management in the hospitalized setting [6].

7. Newer Noninsulin Agents: Maybe?

Given the detrimental effects of hypoglycemia related to insulin therapy and the complexity of administration, studies have also been conducted looking at the role of alternatives to insulin for inpatient diabetes management. Although studies looking at clinical outcomes with incretin therapy in the hospitalized setting are limited, existing trial data suggest this may be a useful addition to or substitute for insulin treatment. A pilot study in 2013 investigated the safety and efficacy of sitagliptin, a DPP4 inhibitor, compared with insulin regimens in general medical/surgical wards [60]. In this trial, 90 patients with diabetes were randomized to one of three arms: sitagliptin only, sitagliptin with daily glargine, and a traditional basal-bolus regimen with daily glargine and bolus lispro insulin. In addition, patients across all three arms received correctional lispro insulin according to a standard sliding scale. Similar improvement was seen across all three groups, including no differences in mean daily blood glucose levels after the first day of treatment ($P = 0.23$) and number of readings within goal blood glucose of 70 to 140 mg/dL ($P = 0.53$). There was no difference in length of stay ($P = 0.78$) or hypoglycemic events ($P = 0.86$) among the three arms, and total daily dose and number of injections were significantly less in the sitagliptin and insulin arm compared with the traditional basal-bolus group ($P < 0.001$). Of note, inclusion in this study was limited to

patients treated for their diabetes with diet alone, oral agents, or insulin therapy at a daily dose ≤ 0.4 U/kg, thus narrowing the clinical applicability of the study findings.

More recently, Pasquel *et al.* [61] went on to further investigate the role of sitagliptin therapy in inpatient management of glucose control among inpatients with type 2 diabetes admitted to general medicine and surgery wards. In this randomized controlled trial, 277 patients were assigned on a 1:1 basis to either the sitagliptin-basal group (daily sitagliptin plus daily glargine) or a more conventional basal-bolus group (mealtime lispro or aspart plus daily glargine). Study investigators found that patients in the sitagliptin-basal group had a similar mean daily blood glucose concentration as those in the basal-bolus group (172 vs 170 mg/dL, respectively), with nonsignificant differences in treatment failure or hypoglycemia rate between the two groups, thus meeting the noninferiority threshold for this trial.

The utility of incretin-based therapy is further supported in an editorial by Schwartz and DeFronzo in 2013 addressing the use of glucagon-like peptide-1 (GLP-1) receptor agonist therapy [62]. Although long considered the gold standard for inpatient management of diabetes by many, Schwartz and DeFronzo proposed that the association of insulin with hypoglycemia and data showing lack of mortality benefit call this role of insulin into question. They argue that, in contrast, GLP-1 agonist therapy would not carry a similar hypoglycemia risk because of the glucose-mediated stimulation of insulin release and inhibition of glucagon secretion [63, 64]. Of note, this opinion is founded on studies among critically ill patients, and its relevancy in the non-ICU setting is less clear.

In terms of efficacy, multiple studies have found treatment with GLP-1 or GLP-1 receptor agonist therapy is comparable with insulin in terms of glycemic control, and even allows for lower insulin dosing if these medications are used concurrently [65–69]. Studies also suggest an impact of GLP-1 therapy on several cardiovascular parameters, including improved left ventricular ejection fraction and endothelial function [70–72]; however, other studies have failed to show a similar effect on left ventricular ejection fraction [69, 73]. Given the dearth of trials looking at clinical outcomes, further study is needed looking at GLP-1 receptor agonist therapy among hospitalized patients. Thus far, however, data regarding incretin-based therapy support the use of these agents for achieving glycemic control in the inpatient setting, especially considering the additional benefit of reduced provider burden in terms of less frequent glucose monitoring and dose titrations [74].

8. Special Circumstances

The use of enteral or parental feeding poses an additional challenge to inpatient glycemic control, with hyperglycemia commonly associated with these forms of nutrition. This has, in turn, been linked to greater inpatient mortality as demonstrated by a prospective study by Oliveira *et al.* [75], which looked at mortality rates among noncritically ill inpatients across 19 hospitals in Spain receiving total parenteral nutrition (TPN). After adjusting for multiple factors, including nutritional state, presence of diabetes, and insulin or steroid use, logistic regression analysis of data collected from 605 patients showed that mean blood glucose levels >180 mg/dL while receiving TPN were associated with a 5.6 times greater mortality risk than levels <140 mg/dL (95% CI, 1.47 to 21.4 mg/dL). For treatment, adding regular insulin to TPN has been a successful strategy to control hyperglycemia, and recommended formulas for calculating dosing are available [76].

Management of hyperglycemia associated with continuous enteral feedings has proven challenging, and few studies are available. However, one was a randomized controlled trial conducted by Korytkowski *et al.* [77]. For this trial, a regimen of sliding-scale regular insulin alone was compared with one with sliding-scale regular insulin and glargine, with 25 inpatients randomized to each group. Although glycemic control was similar between the two groups, 12 patients receiving only sliding-scale regular insulin required the addition of NPH insulin because of persistent hyperglycemia, an intervention not needed among any of those in the group also receiving glargine. Total daily insulin doses were similar between the groups, as was frequency of hypoglycemia. These results support the role of longer-acting

basal insulin in the management of blood glucose levels among those patients receiving enteral feeding.

Another common factor complicating management of blood sugar among hospitalized patients is the prevalent use of glucocorticoids as treatment of a host of conditions known to be associated with hyperglycemia even among those without diabetes [78, 79]. To better characterize the insulin needs of this population, Spanakis *et al.* [80] conducted a chart review of 58 hospitalized patients with diabetes and found that, independent of age, race, body weight, renal function, or disease type, among several other variables, over half the patients remained hyperglycemic throughout their admission ($n = 38$). Those patients that did achieve normoglycemia had similar requirements for basal insulin as those who remained hyperglycemic (23.6 vs 20.1 U, respectively; $P = 0.35$). However, their nutritional insulin requirements were significantly higher (45.5 vs 20.1 U, $P < 0.001$), with lower correction insulin needs (5.8 vs 13.0 U, $P < 0.001$) than their hyperglycemia counterparts, respectively. Overall, their total daily doses of insulin were similar per kilogram between the two groups. Although limited by sample size, and because formal insulin dosing studies have not yet been performed, these findings do suggest nutritional insulin, as opposed to correction, should be made a priority when determining regimens for glucose management in patients on glucocorticoid therapy.

9. Moving Forward

Current guidelines based on studies presented here suggest maintaining fasting glucose values in the 100 to 140 mg/dL range and nonfasting levels <180 mg/dL [1]. Although the clinical impact of hyperglycemia among hospitalized patients has been well established, with multiple studies demonstrating increased morbidity and mortality [12, 81–83], the optimal medical management of diabetes in the inpatient setting has been extensively studied, but not yet definitively established [1, 2, 6, 84]. Insulin is still considered the mainstay of treatment of inpatient glucose control [85], and several trials have been conducted evaluating different regimens, with most data supporting the use of basal insulin (either analog or human) along with either prandial and correctional boluses compared with sliding scale only as described in the Basal Plus trial [7, 36, 37, 43]. More data are needed, however, looking at the clinical outcomes for insulin therapy, including patients without known diabetes. Given the known association of insulin with hypoglycemia, and the detrimental effect such episodes have on morbidity and mortality [44, 86], along with concerns regarding the rigorous blood sugar monitoring and dose adjustments required with insulin therapy [74], the utility of insulin alternatives has been investigated. Metformin, sulfonylureas, and thiazolidinediones have a number of contraindications to use, which often limit their utility in the inpatient setting with critically ill patients [56–58]. Incretin-based therapies have demonstrated promising results toward glycemic control without associated hypoglycemia, and further randomized controlled trials, specifically looking at the role of GLP-1 receptor agonist therapy, are warranted [62, 64, 73, 74, 85, 87, 88]. Thus far, however, there are no long-term data regarding the safety of incretin-based treatment. This raises the question of how effectively risk-benefit ratios can be compared between this therapy and insulin, which benefits from decades of safety data. Given the known negative impact of hypoglycemia and demonstrated association of hypoglycemia with insulin, there is an increased urgency to exploring this question.

One approach to achieving target glycemic control that is gaining attention is an automated closed-loop system for insulin delivery. Also known as the artificial pancreas, this delivery system uses a computerized algorithm by which insulin is either increased or decreased according to subcutaneous glucose sensors. Thabit *et al.* [89] investigated the safety and efficacy of this system compared with traditional subcutaneous insulin delivery in a 2017 controlled trial. For this study, 40 general ward inpatients with type 2 diabetes on insulin therapy were randomized on a 1:1 basis to treatment with the closed-loop insulin delivery system or conventional therapy according to local clinical guidelines. After a 72-hour period, 59.8% of time in the closed-loop system was spent in the target glucose range (100 to 180 mg/dL)

compared with 38.1% in the conventional control group. This led study investigators to conclude that the artificial pancreas was indeed a safe and effective alternative to traditional subcutaneous therapy among noncritically ill inpatients with type 2 diabetes receiving insulin; however, additional factors warrant consideration before translating these findings to a more realistic clinical setting. As described in an editorial response by Rayman [90], barriers to applying the closed-loop system to inpatient practice include limited familiarity among health care professionals with this intervention and potential safety issues that may arise with larger populations and over a longer period of time. Nevertheless, this trial serves as another example of the promising trajectory of inpatient diabetes management, and the value in continuing to investigate additional and alternative approaches to our traditional approach with insulin.

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